

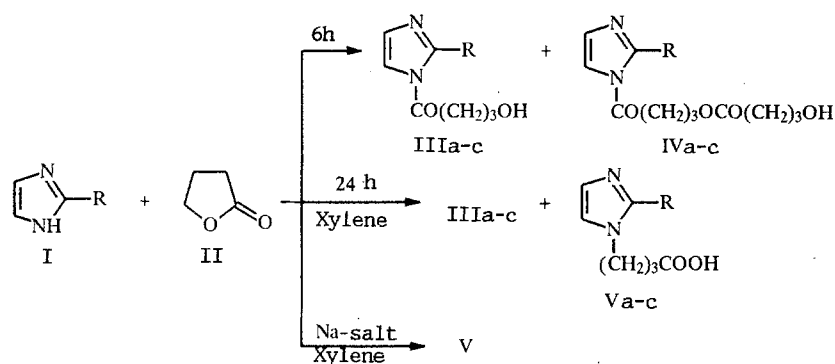
# REACTION OF IMIDAZOLE AND ITS 2-ALKYL DERIVATIVES WITH $\gamma$ -BUTYROLACTONE

O. K. Shevchenko, A. T. Ayupova, and G. G. Galust'yan

*Reaction of imidazole with  $\gamma$ -butyrolactone gives N-alkylation and N-acylation products depending upon the reaction conditions.*

It is known that condensation of benzimidazolin-2-ones with  $\gamma$ -butyrolactone in the presence of aluminum chloride takes place at a benzene ring C-carbon to form C-carboxyalkyl derivatives [1-3]. N-Carboxyalkyl derivatives can be obtained by use of the sodium salts of benzimidazolin-2-ones [4, 5]. N-Carboxyalkyl derivatives of benzoxazolinone and benzoxazolinethione can be prepared in analogous conditions [6].

In this work we have studied the condensation of imidazole and 2-alkyl derivatives with  $\gamma$ -butyrolactone. Electrophilic substitution of imidazoles can occur at the N or C atoms. The most suited to electrophilic attack is evidently the pyridine nitrogen atom. In turn,  $\gamma$ -butyrolactone can react with fission of the acyl-oxygen or alkyl-oxygen bond depending on the conditions [7]. We have shown that refluxing a 1:1 mixture of imidazole I and  $\gamma$ -hydroxybutyrates of ( $\gamma$ -hydroxybutyryl)-imidazoles IV. Apparently, the high reaction temperature (220°C) leads to the addition of a second molecule of  $\gamma$ -butyrolactone to form IV. Increasing the ratio of imidazole to  $\gamma$ -butyrolactone to 1:50 or 1:100 and prolonged heating (18-20 h) leads to extensive tarring. Attempts to distil the tarred reaction mixture in vacuo gave a small amount of polymer. Prolonged heating (24 h) of imidazole and  $\gamma$ -butyrolactone in the ratio 1:1 in xylene (140°C) gives both N-acylation products III and the N-alkylated  $\gamma$ -imidazolylbutyric acid V. Compounds III and V are formed in the ratio 1:1 under these conditions.



We have studied the reaction of dry imidazole sodium salts with a small excess of  $\gamma$ -butyrolactone in DMF; an aprotic solvent allowing dissociation of the imidazole salt. Under these conditions only N-alkylation products V were obtained in 40% yield, the reaction being accompanied by marked tarring. If carried out in xylene the yield of acid V is increased to 60% with no tarring. The acids V were identified through their methyl esters VI (see Table 1).

In the IR spectrum of V the carbonyl group absorption is seen at 1725 and the hydroxyl at 2500-3200  $\text{cm}^{-1}$ . The carbonyl group on the nitrogen atom in III shows absorption at 1500 and the hydroxyl at 3200  $\text{cm}^{-1}$ .

Institute for the Chemistry of Plant Substances, Uzbekistan Academy of Sciences, Tashkent 700170. Translated from *Khimiya Geterotsiklicheskikh Soedinenii*, No. 11, pp. 1491-1493, November, 1992. Original article submitted September 23, 1991.

TABLE 1. Data for the Imidazoles III-VI

Compound	Empirical formula	Mp, °C*	M <sup>+</sup>	R <sub>f</sub>	Yield, % (method)
IIIa	C <sub>7</sub> H <sub>10</sub> N <sub>2</sub> O <sub>2</sub>	124...125	154	0,24	47 (A), 16 (B)
IIIb	C <sub>8</sub> H <sub>12</sub> N <sub>2</sub> O <sub>2</sub>	—	168	0,31	37 (A), 10 (B)
IIIc	C <sub>9</sub> H <sub>14</sub> N <sub>2</sub> O <sub>2</sub>	—	182	0,37	22 (A), 5 (B)
IVa	C <sub>11</sub> H <sub>16</sub> N <sub>2</sub> O <sub>4</sub>	185...186	240	0,13	10 (A)
IVb	C <sub>12</sub> H <sub>18</sub> N <sub>2</sub> O <sub>4</sub>	—	254	0,21	5 (A)
IVc	C <sub>13</sub> H <sub>20</sub> N <sub>2</sub> O <sub>4</sub>	—	268	0,30	3 (A)
Va	C <sub>7</sub> H <sub>10</sub> N <sub>2</sub> O <sub>2</sub>	138	—	0,44	63 (C), 14 (B)
Vb	C <sub>8</sub> H <sub>12</sub> N <sub>2</sub> O <sub>2</sub>	198	—	0,47	35 (C), 8 (B)
Vc	C <sub>9</sub> H <sub>14</sub> N <sub>2</sub> O <sub>2</sub>	152	—	0,51	27 (C), 5 (B)
VIa	C <sub>8</sub> H <sub>12</sub> N <sub>2</sub> O <sub>2</sub>	—	168	0,29	30
VIb	C <sub>9</sub> H <sub>14</sub> N <sub>2</sub> O <sub>2</sub>	—	182	0,33	18
VIc	C <sub>10</sub> H <sub>16</sub> N <sub>2</sub> O <sub>2</sub>	—	196	0,38	20

\*A dash indicates that the substance is an oil.

The mass spectra of III, IV, and VI show strong molecular ion peaks (M<sup>+</sup>) (Table 1) corresponding to the structures proposed. PMR spectral data (see Experimental) supported the structures of III, IV, and V.

Hence the course of the reaction of imidazole with  $\gamma$ -butyrolactone is decided by the reaction conditions. If the substrate is the imidazole anion, N-alkylation occurs and if the neutral molecule both N-alkylation and N-acylation can occur. In other words, the fission of the  $\gamma$ -butyrolactone at the acyl-oxygen or alkyl-oxygen is determined by the acid-base properties of the imidazole [8]. The increased nucleophilicity of imidazole, which occurs either through use of the imidazole anion or variation of temperature [9], leads principally to fission of the alkyl-oxygen bond of  $\gamma$ -butyrolactone.

## EXPERIMENTAL

IR spectra were recorded for KBr tablets on a UR-20 spectrophotometer and UV spectra on a Hitachi EPS-3T spectrometer using ethanol solvent. PMR spectra were taken on a Jeol C-60HL using HMDS internal standard. Purity and identity of the compounds were controlled by TLC on Silufol UV-254 plates in chloroform-methanol-acetic acid (10:9:1). For preparative column separation L40/100 micron silica gel was used.

**Reaction of Imidazoles Ia-c with  $\gamma$ -Butyrolactone.** A. A mixture of imidazole (3.4 g, 0.05 mole) and  $\gamma$ -butyrolactone (4 ml, 0.05 mole) was refluxed for 6 h, cooled, and treated with isopropanol (50 ml). The precipitated crystals were filtered off and recrystallized from isopropanol (30 ml) to give the  $\gamma$ -hydroxybutyrate IIIa (3.7 g, 47%) (C<sub>7</sub>H<sub>10</sub>N<sub>2</sub>O<sub>2</sub>) as light yellow crystals with mp 124-125°C and R<sub>f</sub> 0.24. The fraction of the precipitate insoluble in refluxing isopropanol was recrystallized from water to give IVa (1.16 g, 10%) (C<sub>11</sub>H<sub>16</sub>N<sub>2</sub>O<sub>4</sub>) as white crystals with mp 185-186°C and R<sub>f</sub> 0.13. Compounds IIIb, c (C<sub>8</sub>H<sub>12</sub>N<sub>2</sub>O<sub>2</sub> and C<sub>9</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub>) and IVb, c (C<sub>12</sub>H<sub>18</sub>N<sub>2</sub>O<sub>4</sub> and C<sub>13</sub>H<sub>20</sub>N<sub>2</sub>O<sub>4</sub> correspondingly) were obtained from the reaction mixture with isopropanol as an oil which separated on L40/100 nonbonded silica gel plates using chloroform-methanol (1:2) eluent. PMR spectra of IIIa-c (CDCl<sub>3</sub>): 3.9-4.25 (2H, m, COCH<sub>2</sub>), 1.95-2.05 (2H, m, CH<sub>2</sub>OH), 2.2-2.35 ppm (2H, m, CH<sub>2</sub> chain). PMR spectra of IVa-c (CDCl<sub>3</sub>): 3.9-4.2 (2H, m, CO-CH<sub>2</sub>), 1.9-2.05 (2H, m, CH<sub>2</sub>OH), 2.2-2.35 (2H, m, CH<sub>2</sub> chain), 4.1-4.4 ppm (4H, m, CH<sub>2</sub>-O-CO-CH<sub>2</sub>).

B. Imidazole (3.4 g, 0.05 mole) and  $\gamma$ -butyrolactone (4.0 g, 0.05 mole) in xylene (10 ml) were placed in a flask with reflux condenser. The mixture was heated for 24 h at 140°C, evaporated on a water bath and the oil obtained treated with isopropanol (50 ml). TLC showed the precipitate (2.41 g) to contain the  $\gamma$ -hydroxybutyrate IIIa (R<sub>f</sub> 0.24) and the alkylation product Va (R<sub>f</sub> 0.44). Chromatography of 1.0 g of mixture on a silica gel column using chloroform-methanol eluent (5:2) gave initially IIIa (0.61 g, 16%) as light yellow crystals with mp 124-125°C (isopropanol) and R<sub>f</sub> 0.24. Va (0.54 g, 14%) (C<sub>7</sub>H<sub>10</sub>N<sub>2</sub>O<sub>2</sub>) was then eluted as white crystals with mp 138°C (butanol) and R<sub>f</sub> 0.44.

Compounds IIIb, c and Vb, c (C<sub>8</sub>H<sub>12</sub>N<sub>2</sub>O<sub>2</sub>) (see Table 1) were obtained similarly.

C. Metallic sodium (2.3 g, 0.1 mole) was added portionwise with stirring to absolute alcohol (40 ml) in a round bottomed flask fitted with a condenser and calcium chloride tube. After complete solution of the sodium the imidazole (6.8 g, 0.1 mole) was added portionwise over 20 min. The alcohol was evaporated to dryness,  $\gamma$ -Butyrolactone (8.4 ml, 0.11 mole) and xylene (DMF) (20 ml) were added to the sodium salt obtained and the product was heated with stirring for 2.5 h. The xylene was evaporated on a water bath and the residue neutralized using a 3-5% HCl solution ( $V = 80$  ml) until weakly acid. The product was evaporated to one-third volume and the sodium chloride filtered off and washed with absolute alcohol (20 ml). The filtrate was treated with an equal volume of butanol. The precipitate formed on standing was filtered and recrystallized from butanol (20 ml) to give Va (8.07 g, 63%).

Vb, c were prepared similarly. Treatment of the acids Va, b, c with diazomethane gave the methyl esters VIa, b, c ( $C_8H_{12}N_2O_2$ ,  $C_9H_{14}N_2O_2$ , and  $C_{10}H_{16}N_2O_2$ , respectively) (see Table 1). PMR spectra of Va-c ( $CDCl_3$ ): 4.05-4.5 (2H, t, N- $CH_2$ ), 2.0-2.2 (2H, m,  $CH_2$ -chain), 2.25 (2H, t,  $CH_2COOH$ ), 9.4 ppm (1H, s, COOH).

## REFERENCES

1. M. N. Kosyakovskaya and Ch. Sh. Kadyrov, Uzb. Khim. Zh., No. 3, 29 (1966).
2. Ch. Sh. Kadyrov, M. N. Kosyakovskaya, and M. R. Yagudaev, Uzb. Khim. Zh., No. 3, 34 (1968).
3. Ch. Sh. Kadyrov and S. S. Khalikov, Khim. Prir. Soedin., No. 3, 369 (1983).
4. S. S. Khalikov, Ch. Sh. Kadyrov, A. T. Ayupova, and L. V. Molchanov, Khim. Getrotsikl. Soedin., No. 11, 1517 (1985).
5. A. T. Ayupova, Ch. Sh. Kadyrov, and K. Seitanidi, Khim. Geterotsikl. Soedin., No. 2, 235 (1974).
6. Zh. Eshimbetov, V. A. Barashkin, N. A. Aliev, Ch. Sh. Kadyrov, and R. Razakov, Khim. Geterotsikl. Soedin., No. 4, 464 (1973).
7. K. Ingold, Theoretical Basis of Organic Chemistry [Russian translation], Mir, Moscow (1973), p. 936.
8. A. F. Pozharskii, Theoretical Basis of the Chemistry of Heterocycles [in Russian], Khimiya, Moscow (1985), p. 136.
9. G. I. Koldobskii and V. A. Ostrovskii, Khim. Geterotsikl. Soedin., No. 5, 579 (1988).